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Synthesis of a Pilot-Scale Library of 4-amino-2-(diethylaminomethyl)phenol (ADOC) Analogues for Testing of Organophosphate-Inhibited Acetylcholinesterase Reactivation Ability

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14. ABSTRACT

Herein we present a short synthetic method for the generation of 4-amino-2-(diethylaminomethyl)phenol (ADOC) analogs **4a-c** and **6a-c** from commercially available and inexpensive acetaminophen (**2**). The method was used to prepare and make available a pilot-scale library of analogs for *in vitro* biological evaluation in the USAMRICD's multi-agent screen for nerve agent-inhibited acetylcholinesterase reactivation. Our hope is that this method will facilitate SAR studies directed toward the development ADOC-based, non-oxime therapies for treating nerve agent intoxication.

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ADOC, amino-(diethylaminomethyl)phenol, SAR, ADOC analogs, acetaminophen, acetylcholinesterase, reactivator, non-oxime

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Background and Introduction

4-amino-2-(diethylaminomethyl)phenol (ADOC) was disclosed as a reactivator of nerve agent inhibited acetylcholinesterase (Figure 1).[1-2] Previous structure activity relationship (SAR) studies of this molecule helped to elucidate the role of the hydroxyl, diethylamino and NH_2 amino groups in the molecule's reactivation activity.[2] The hydroxyl group appears essential for reactivation, as methylation of the hydroxyl abolishes reactivation activity. The diethylamino group seems to function in both reactivation and molecular recognition for binding in the active site. Reduction or increase in steric bulk around the benzylic nitrogen serves to reduce activation potential. Similarly, the NH_2 amino group appears to be involved in active site binding and recognition where addition of sterically bulky groups attenuates reactivation.

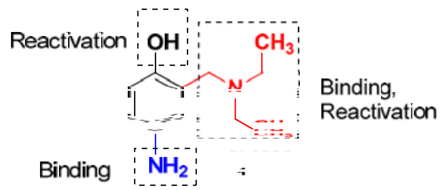
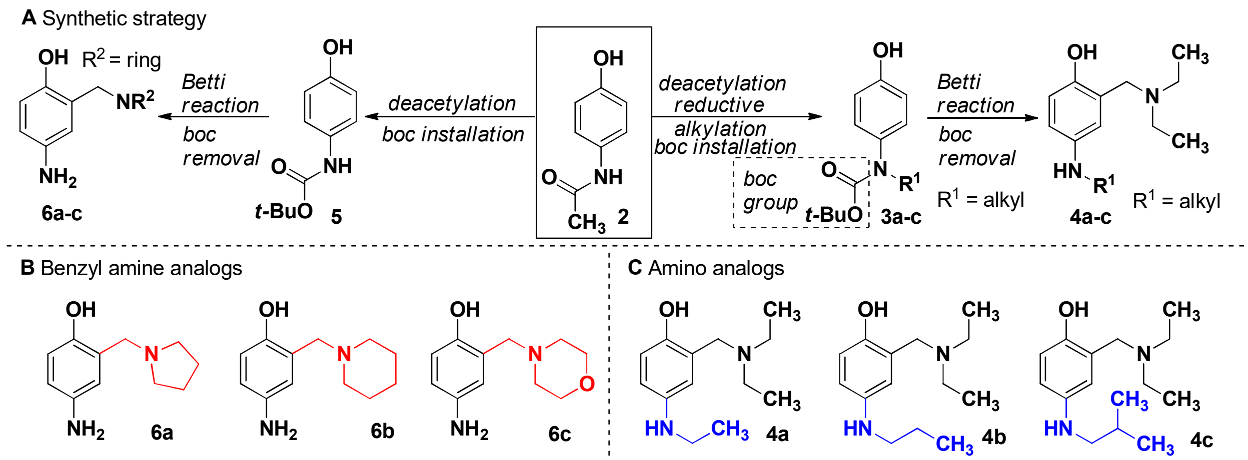


Figure 1. Structure of ADOC (**1**) and brief summary of SAR

In order to support additional SAR studies of ADOC (**1**) we developed a synthetic method to generate structural analogs, beginning with commercially available and inexpensive acetaminophen (Tylenol) (**2**) (Scheme 1A). Because of the apparent importance of the hydroxyl group, our efforts focused on developing a route to modify the NH_2 amino and benzyl amino groups in order to further investigate the effect of structural modifications at these locations on reactivation of nerve agent-inhibited acetylcholinesterase (Scheme 1B and 1C). Alkylated analogs **4a-c** were accessed in 5 steps from **2**. The *tert*-butylcarbamate group ("boc") was chosen to facilitate isolation and purification of synthetic intermediates and the final compounds. Alkylation of the NH_2 amino group was readily achieved by a one-pot reductive alkylation of *p*-aminophenol (**8**, Scheme 3).[3] The requisite benzyl amine was next installed by an efficient electrophilic aromatic substitution reaction between phenols **3a-c**, *N,N*-diethylamine, and formaldehyde (the Betti reaction).[2] Finally, the boc group was readily cleaved under acidic conditions to furnish the desired analogs. We initially sought to generate benzyl amino analogs **6a-c** through a short 2-step synthetic sequence from a Betti reaction on **2** with the requisite secondary amine, followed by a deacetylation reaction. The Betti reaction proceeded smoothly; however, deacetylation under acidic conditions worked poorly (discussed below). We were happy to find that boc-protected phenol **5** provided access to the title compounds **6a-c.**

Scheme 1: Synthesis of ADOC (**1**) and analogs from Tylenol (**2**).

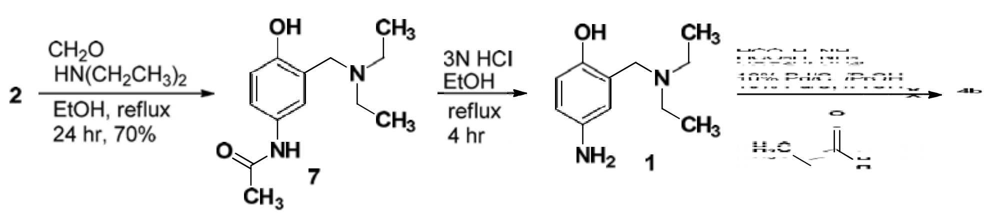


Results and Discussion

Preparation of *N*-alky analogs **4a-c**

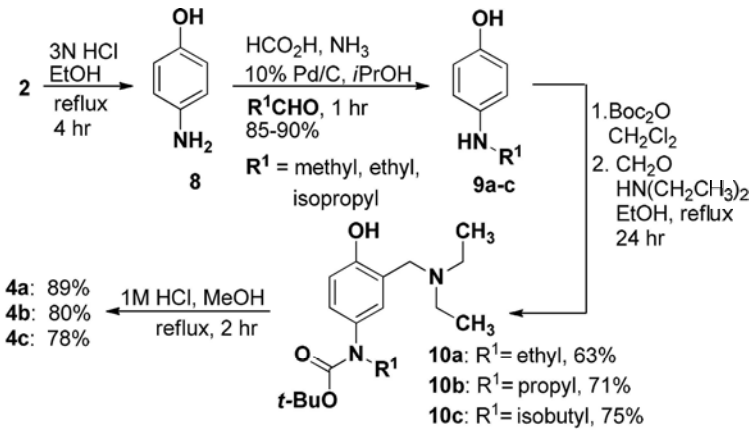
Our initial efforts focused on a 3-step route to generate analogs **4a-c** from acetaminophen (**2**), whereby the desired compounds would be achieved directly by an alkylation of ADOC (**1**) (Scheme 2). Although **1** was readily obtained from **2** by a Betti reaction with *N,N*-diethylamine, followed by deacetylation, we found that direct alkylation of **1** with propionaldehyde produced a mixture of undesired compounds, confirmed by ^{1}HNMR, which prompted us to pursue an alternative method for generating **4a-c**.

Scheme 2. Initial efforts to synthesize **4b**.



Hypothesizing that the basic benzylamine group of **1** may be interfering with the proposed imine intermediate produced in the alkylation step, we next attempted alkylating first, followed by installation of the *N,N*-diethylamino group second (Scheme 3). Deactylation of **2** provided *p*-aminophenol (**8**) which smoothly underwent alkyation to furnish anilines **9a-c**. Next, since the Betti reaction proceeds through addition of the starting phenol to an iminum ion, we chose to install a *tert*-butylcarbamate ("boc") group to avoid any potential unwanted reactivity from the nitrogen of **9a-c**. In addition, installation of the boc group would likely facilitate any purification steps and could be easily removed as a final step. We were delighted to find that **9a-c** provided penultimate intermediates **10a-c**. Attempts were next made to remove the boc group under acidic conditions with trifluoroacetic acid (TFA). Although TFA did indeed remove the boc group, it also generated a side product which we were unable to separate from the desired analogs **4a**-**c** (not shown). Ultimately we found that the boc group could be removed under mildly acidic conditions with HCl to furnish **4a-c**.

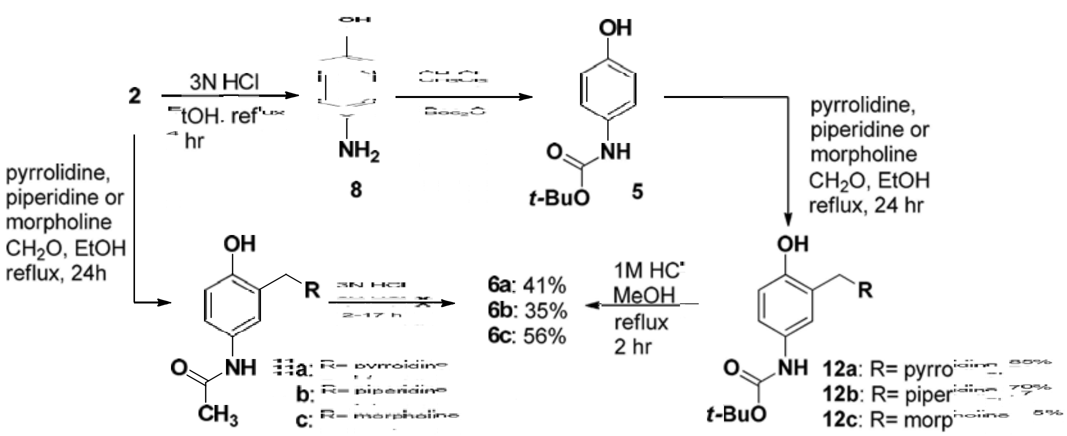
Scheme 3. Synthesis of analogs **4a-c**.



Preparation of benzylamino analogs **6a-c**

Our initial efforts focused on the synthesis of **11a-c** as they would have provided the most direct route to analogs **6a-c** (Scheme 4). Intermediates **11a-c** were readily obtained; however, we were unable to completely remove the acetyl group under acidic conditions and in every instance observed a mixture of unreacted starting material, degraded starting material, and some desired product. Based on our success with the synthesis of **4a-c** (Scheme 3), we opted for a route involving boc-protected intermediate **5,** which we were happy to discover was easily elaborated to furnish the desired compounds.

Scheme 4. Synthesis of benzylamino analogs **6a-c.**



Conclusion

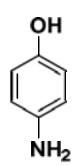
Herein we presented a short synthetic method for the generation of ADOC analogs **4a-c** and **6a-c** from commercially available and inexpensive acetaminophen (**2**). The method was used to prepare and make available a pilot-scale library of analogs for *in vitro* biological evaluation in the USAMRICD's multi-agent screen for nerve agent-inhibited acetylcholinesterase reactivation. Our hope is that this method will facilitate SAR studies directed toward the development ADOC-based, non-oxime therapies for treating nerve agent intoxication.

Experiments

Materials: Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of room air with stirring.

Instrumentation: ^{1}HNMR spectra were obtained on a 400 MHz Bruker NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS (s, δ 0.0 ppm). Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet), bs (broad singlet). Chromatographic purifications were performed by flash chromatography with Teledyne Isco 4 gram or 12 gram RediSepRf silica gel normal phase columns on a Teledyne Isco Combiflash EZ Prep purification system. Compounds were detected by UV absorbance at 254 nm and 280 nm, as well as evaporative light scattering detection. The eluting solvent for the purification of each compound was determined by thin layer chromatography (TLC) on Millipore aluminum backed slica gel-coated plates (Silica Gel 60, F254) and visualized by UV light at 254 nm.

The following abbreviations are used throughout: room temperature (rt), ethyl acetate (EtOAc), methanol (MeOH), ethanol (EtOH), *tert*-butyloxycarbonyl (boc), dichloromethane (DCM), and triethylamine (TEA), tetrahydrofuran (THF), isopropanol (*i*PrOH)

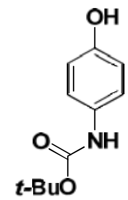


(**8**) *p*-aminophenol

Acetaminophen (**2**) (3.0 g, mmol) was dissolved in 3M HCl in water (15 mL) and refluxed for 4 hours. The reaction was then allowed to cool to room temperature, and the pH was adjusted to ~8 with saturated $NaHCO_3$ and transferred to a separatory funnel. The aqueous layer was extracted 3x with EtOAc. The combined organic fractions were dried of Na_2SO_4, filtered, and concentrated to provide the title compound as a brown solid (1.6 g, 73%). ^{1}HNMR (500 MHz, *d*-DMSO) δ 8.38 (s, 1H), 6.48 (d, J = 8.7 Hz, 2H), 6.42 (d, J = 8.7 Hz, 2H).

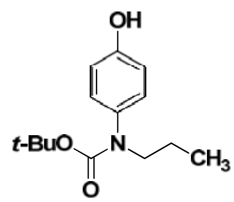
General Experiment A: Preparation of **5** and **3a-c**

p-aminophenol (**8**) (1 equiv.), di-*tert*-butylcarmbamate (1 equiv), TEA (2 equiv), and DCM or THF (0.25 M) were combined, and the mixture was allowed to stir at rt for 24 hours. The reaction was then concentrated *in vacuo*, and the title compounds were either used without further purification or isolated by flash column chromatography.



(**5**) *tert*-butyl (4-hydroxyphenyl)carbamate

The title compound was prepared from *p*-aminophenol (**8**) (0.138 g, 1.3 mmol) according to general experiment A**.** Reaction progress was monitored by TLC using DCM with 5% MeOH and 1%TEA and was complete after 24 hours. The reaction was then concentrated, dried under vacuum to provide a brown solid, and used in the subsequent step without further purification. ^{1}HNMR (500 MHz, *d*-Acetone) δ 8.13 (bs, 1H), 7.36 (m, 2H), 6.79 (d, J = 8.8 Hz, 2H), 1.31 (s, 9H).

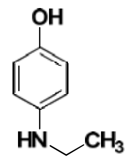


(**3b**) *tert*-butyl (4-hydroxyphenyl)(propyl)carbamate

The title compound was prepared from *p*-aminophenol (0.161 g, 1.06 mmol) according to general experiment A**.** Flash column chromatography with 20%-100% EtOAc:hexanes afforded **3b** as a yellow oil (0.191 mg, 72%). ^{1}HNMR (500 MHz, *d*-DMSO) δ 6.97 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 7.2 Hz, 2H), 3.41 (q, J = 7.2 Hz, 2H), 1.42-1.34 (m, 11H), 0.81 (t, J = 7.4 Hz, 3H).

General Experiment B – Preparation of **9a-c**

Ammonia (7N in MeOH, 2.62 mL, 18.3 mmol, 10 equiv) and formic acid (0.690 mL, 18.3 mmol, 10 equiv) were combined in iPrOH (15 mL) at rt and stirred for about 5 minutes. The resultant ammonium formate was then dissolved in a minimum amount of water (~1.5 mL). To this solution was next added 10% Pd/C (0.06 g, 30% by weight with respect to *p*-aminophenol (**8**)). The mixture was allowed to stir ~5 minutes after which time *p*-aminophenol **(2)** (0.20 g, 1.83 mmol, 1.0 equiv) was added followed by the respective aldehyde (acetaldehyde, propionaldehyde, isobutyraldehyde, 1.83 mmol, 1.0 equiv). The reaction was monitored by TLC and was complete by 1 hour. *i*PrOH was removed *in vacuo*, the reaction contents were taken up in EtOAc and water and the layers were separated. The organic layer was collected, and the aqueous layer was extracted twice more with EtOAc. Combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo* to provide the title compounds **9a-c** as thin yellow oils which were used in subsequent reactions without further purification.

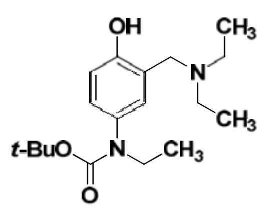


(**9a**) 4-(ethylamino)phenol

The title compound was prepared from *p*-aminophenol (**8**) (0.20 g, 1.83 mmol) according to general experiment B. ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.73 (d, J = 8.2 Hz, 2H), 6.57 (d, J = 8.3 Hz, 2H), 3.12 (q, J = 6.8 Hz, 2), 1.25 (t, J = 7.2 Hz, 3H).

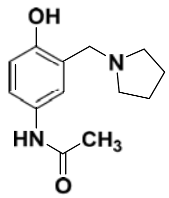
General Experiment C – Preparation of **10a-c**, **11a**, and **12a-c**

Aminophenol **2**, **5**, or **3a-c** (1 equiv), formaldehyde (1.1 equiv), primary or secondary amine (1 equiv), and EtOH (0.5 M) were combined in a round bottom flask, and the mixture was refluxed using a Findenser Super Air Condenser for 24 hours with stirring. The reaction was then allowed to cool, and products were visualized using TLC in a solvent system of DCM with 5% MeOH, 1% TEA. The reaction mixture was then adjusted to pH ~8.0 using saturated sodium bicarbonate followed by the addition of EtOAc. Three extractions were performed on the aqueous layer, and the combined organic layers were collected, dried over Na_2SO_4, concentrated and dried *in vacuo*. The crude reaction mixture was then purified on a 12 g silica flash column at a flow rate of 30 mL/min with a solvent system of DCM with 1% TEA with a gradient of MeOH increasing from 0% to 10% from 0 minutes to 17 minutes followed by a ramp up to 20% MeOH from 17 minutes to 20 minutes. Collections containing product were then concentrated *in vacuo* to provide the target compounds.



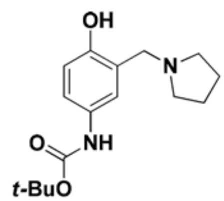
(**10a**) tert-butyl (3-((diethylamino)methyl)-4-hydroxyphenyl)(ethyl)carbamate

The title compound was prepared from aminophenol **3a** (0.117g, 0.493 mmol) according to general experiment C. Flash column chromatography provided **10a** as an oil (0.100g, 63%). ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.95 (bs, 1H), 6.77 (m, 2H), 3.76 (s, 2H), 3.61 (q, J = 7.1 Hz, 2H), 2.64 (q, J = 7.2 Hz, 4H), 1.43 (s, 9H), 1.13 (m, 9H).



(**11a**) *N*-(4-hydroxy-3(pyrrolidin-1-ylmethyl)phenyl)acetamide

The title compound was prepared from acetaminophen (**2**) (1.0g, 1.62 mmol) according to general experiment C. Flash column chromatography provided the title compound as an off white solid. ^{1}HNMR (500 MHz, *d*-Acetone) δ 8.89 (bs, 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.30 (dd, J = 8.6, J = 2.6 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 3.79 (s, 2H), 2.60 (m, 4H), 2.03 (s, 3H), 1.86 (m, 4H).

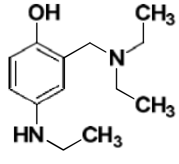


(**12a**) tert-butyl (4-hydroxy-3-(pyrrolidin-1-ylmethyl)phenyl)carbamate

The title compound was prepared from *tert*-butyl (4-hydroxyphenyl)carbamate **5** (0.056g, 0.267 mmol) according to general experiment C. Flash column chromatography provided **12a** as an oil (0.066g, 85%). ^{1}HNMR (500 MHz, *d*-Acetone) δ 8.10 (bs, 1H), 7.30 (s, 1H), 7.21 (m, 1H), 6.64 (d, J = 8.6 Hz, 1H), 3.81 (s, 2H), 2.64 (m, 4H), 1.86 (m, 4H), 1.48 (s, 9H).

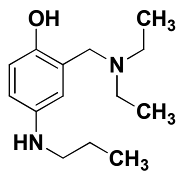
General Experiment D – Boc cleavage

Boc-protected phenol **10a-c** or **12a-c** (0.02-0.05g) was dissolved in 1M HCl in MeOH (3 mL) and allowed to reflux at 85°C for 2 hours with stirring. The reaction mixture was allowed to cool to room temperature and was then adjusted to pH ~8.0 using saturated sodium bicarbonate, and EtOAc was added. Three extractions were performed on the aqueous layer, and the combined organic layers were collected, dried over Na_2SO_4, concentrated and dried *in vacuo*. The crude reaction mixture was then purified on a 12 g silica flash column at a flow rate of 30 mL/min with a solvent system of DCM with 1% TEA with a gradient of MeOH increasing from 0% to 10% from 0 minutes to 17 minutes followed by a ramp up to 20% MeOH from 17 minutes to 20 minutes. The success of the purification was verified by TLC, and fractions containing product were then concentrated under vacuum.



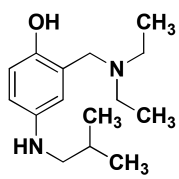
(**4a**) 2-((diethylamino)methyl)-4-(ethylamino)phenol

The title compound was prepared from boc-protected phenol **10a** (0.021g, 0.065 mmol) according to general experiment D. Work-up and concentration *in vacuo* provided ADOC analog **4a** as a brown oil (0.013g, 89%). No purification was required. ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.70 (d, J = 8.6 Hz, 1H), 6.51 (dd, J = 8.5, J = 2.8 Hz, 1H), 6.34 (d, J = 2.7 Hz, 1H), 3.42 (s, 2H), 3.11 (q, J = 7.1 Hz, 2H), 2.63 (q, J = 7.2 Hz, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.12 (t, J = 7.2 Hz, 6H); ^{13}CNMR (125 MHz, *d*-Acetone) 149.5, 142.1, 122.7, 116.0, 113.3, 112.7, 56.8, 46.1, 38.8, 14.2, 10.7; MS (ESI) *m/z* calculated for $C_{11}H_{23}N_2O$ (M+H) 223.3, found 223.2.



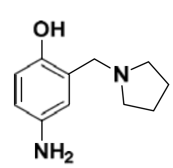
(**4b**) 2-((diethylamino)methyl)-4-(propylamino)phenol

The title compound was prepared from boc-protected phenol **10b** (0.021g, 0.062 mmol) according to general experiment D. Work-up and concentration *in vacuo* provided ADOC analog **4b** as a brown oil (0.012g, 80%). No purification was required. ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.69 (d, J = 8.5 Hz, 1H), 6.50 (dd, J = 8.6, J = 2.7 Hz, 1H), 6.33 (d, J = 2.6 Hz, 1H), 3.71 (s, 2H), 3.03 (t, J = 7.1 Hz, 2H), 2.63 (q, J = 7.2 Hz, 4H), 1.63 (m, 2H), 1.12 (t, J = 7.2 Hz, 6H), 1.05 (t, J = 7.4 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) 150.1, 141.3, 122.8, 116.6, 113.7, 113.5, 57.12, 47.1, 46.3, 22.9, 11.7, 11.2; MS (ESI) *m/z* calculated for $C_{14}H_{25}N_2O$ (M+H) 237.4, found 237.2.



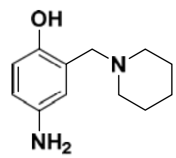
(**4c**) 2-((diethylamino)methyl)-4-(isobutylamino)phenol

The title compound was prepared from boc-protected phenol **10c** (0.025g, 0.071 mmol) according to general experiment D. Work-up and concentration *in vacuo* provided ADOC analog **4c** as a brown oil (0.014g, 78%). No purification was required.^{1}HNMR (500 MHz, $CDCl_3$) δ 6.69 (d, J = 8.6 Hz, 1H), 6.50 (dd, J = 8.6, J = 2.6 Hz, 1H), 6.32 (d, J = 2.6 Hz, 1H), 3.71 (s, 2H), 2.87 (d, J = 6.8 Hz, 2H), 2.63 (q, J = 7.2 Hz, 4H), 1.88 (m, 1H), 1.12 (t, J = 7.2 Hz, 6H), 1.05 (d, J = 6.7 Hz, 6H); ^{13}CNMR (125 MHz, *d*-Acetone) 149.9, 141.5, 122.7, 116.8, 113.7, 113.5, 57.0, 53.1, 46.3, 28.1, 20.6, 11.1; MS (ESI) *m/z* calculated for $C_{15}H_{27}N_2O$ (M+H) 251.4, found 251.4.



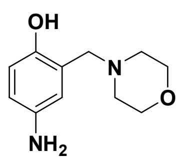
(**6a**) 4-amino-2-(pyrrolidin-1-ylmethyl)phenol

The title compound was prepared from boc-protected phenol **12a** (0.030g, 0.103 mmol) according to general experiment D. Flash column chromatography provided ADOC analog **6a** as a brown oil (0.008g, 41%). ^{1}HNMR (500 MHz, *d*-Acetone) δ 6.47 (s, 2H), 6.39 (s, 1H), 3.68 (s, 2H), 2.85 (bs, 2H), 2.58 (m, 4H), 1.80 (m, 4H); ^{13}CNMR (125 MHz, *d*-Acetone) 149.8, 140.2, 123.1, 119.6, 115.8, 114.9, 58.6, 53.2, 23.3; MS (ESI) *m/z* calculated for $C_{11}H_{17}N_2O$ (M+H) 193.3, found 193.3.



(**6b**) 4-amino-2-(piperidin-1-ylmethyl)phenol

The title compound was prepared from boc-protected phenol **12b** (0.025g, 0.082 mmol) according to general experiment D. Flash column chromatography provided ADOC analog **6b** as a brown oil (0.006g, 35%). ^{1}HNMR (500 MHz, *d*-Acetone) δ 6.48 (s, 2H), 6.37 (s, 1H), 3.54 (s. 2H), 2.86 (bs, 4H), 1.61 (m, 4H), 1.50 (m, 2H); ^{13}CNMR (125 MHz, *d*-Acetone) 149.6, 146.6, 122.0, 119.4, 115.2, 114.6, 61.9, 53.7, 26.1, 23.9; MS (ESI) *m/z* calculated for $C_{12}H_{19}N_2O$ (M+H) 207.3, found 207.2.



(**6c**) 4-amino-2-(morpholinomethyl)phenol

The title compound was prepared from boc-protected phenol **12c** (0.050g, 0.162 mmol) according to general experiment D. Flash column chromatography provided ADOC analog **6c** as a brown oil (0.019g, 56%). ^{1}HNMR (500 MHz, *d*-Acetone) δ 6.51 (s, 2H), 6.42 (s, 1H), 3.69 (bs, 4H), 3.59 (s, 2H), 2.52 (bs, 4H); ^{13}CNMR (125 MHz, *d*-Acetone) 153.4, 143.7, 121.3, 120.4, 119.8, 115.7, 66.4, 61.05, 52.8; MS (ESI) *m/z* calculated for $C_{11}H_{17}N_2O_2$ (M+H) 209.3, found 209.1.

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